

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214375Orig1s000

PRODUCT QUALITY REVIEW(S)

**NDA 214375 Resubmission Xenoview
OPQ Integrated Quality Assessment (IQA)**

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NDA Executive Summary

1. Application/Product Information

NDA Number.	214375 Resubmission after Complete Response and Clock Extension to Dec 30, 2022		
Applicant Name	Polarean Inc Durhem, NC 27523		
Drug Product Name	Xenoviev (xenon Xe 129 hyperpolarized)		
Dosage Form.	Gas		
Proposed Strength(s)	75 mL of 100% polarized ¹²⁹ Xe ((b) (4) ml of ¹²⁹ Xe at a target (b) (4) % degree of overall polarization)		
Route of Administration	Dose delivery bag, Respiratory (Inhalation)		
Maximum Daily Dose	Dose equivalent (DE) volume ≥ 75 mL in 1000 mL		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b) (4)		
Drug Product Description	1 L bag volume of gas (b) (4) (b) (4) 75 mL) is hyperpolarized ¹²⁹ Xe and q.s.'d with (b) (4) N ₂ . In terms of percentages, the target dose is (b) (4) % hyperpolarized ¹²⁹ Xe and (b) (4) % N ₂ .		
Co-packaged product information	N/A		
Device information:	Polarean HPX Hyperpolarizer		
Storage Temperature/ Conditions	25 °C (77°F)		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Anne Marie Russell	Danae Christodoulou
	<i>Drug Product/ Labeling</i>	Anne Marie Russell	Danae Christodoulou



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	<i>Manufacturing</i>	Krishna Ghosh	Vidya Pai
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i> CDRH	See consults	See consults
	<i>RBPM</i>	Anika Lalmansingh	
	<i>ATL</i>	Eldon E. Leutzinger	
Consults	CDRH (Dan Krainak, Cecily Jones, Ningzhi Li)		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

Xenoview has an expiry of 5 minutes after DE is determined (during QC) at 25⁰C.

b. Additional Comments for Action

A PMC (#4324-2) has been agreed to by Polarean on December 15, 2022 to be fulfilled in one year.

4. Basis for Recommendation:

All Drug Product CMC issues from the CR letter of 10/05/2021 are Resolved.

Xenoview has an expiry of 5 minutes after DE is determined (during QC) at 25⁰C and proven to be reasonable considering the fragility of hyperpolarized states and based on stability results. That it is meaningful in terms of the capability that the patient ventilation procedure can be executed by a Polarean trained technician within 5 minutes of the DE determination was confirmed by the OND clinical team.

All drug and device facilities and inspection issues are Resolved. One of the observations from the PAI inspection required new analytical method validations,



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(b) (4)
successfully and provided adequate data. Critical issues (b) (4)

(b) (4) are handled under separate cover. LOAs, one submitted by Polarean and another by (b) (4) authorizing the FDA to communicate with both parties regarding CMC manufacturing issues, aiding in the resolution of the issues in the (b) (4) DMF (there were three reassessment communications).

¹²⁹Xe (b) (4) has currently a single supplier (b) (4); see Qualified Supply Chain and Distribution Plan under Additional Lifecycle Comments). For this supplier and any future suppliers there is need for a **designated responsible party** for supplier qualification together with a specified procedure to qualify suppliers, and an acceptance procedure (with specifications). **The issues impacting the cGMP supplier qualification (b) (4) will be addressed in a Post Marketing Commitment (PMC # 4324-2). With the PMC in place, the (b) (4) DMF supports Polarean's Xenoview NDA. On Dec 15, 2022, Polarean agreed to PMC #4324-2 to be fulfilled in one year. OPMA will review the fulfillment of the PMC.**

PMC: 4324-2

DESCRIPTION: (b) (4) (Xe-129 (b) (4) gas) - Supplier Qualification, Acceptance Procedure and Specifications

Goal of the Study:

For (b) (4) enriched xenon Xe-129 gas, a Quality Product Agreement (QPA) or PMC is needed to:

- designate Polarean as the responsible party for supplier qualification
- specify the procedure to qualify suppliers
- 4324-2specify the acceptance procedure (b) (4) received from qualified suppliers
- provide specifications (b) (4)

Qualification of the current supplier (b) (4) is also needed, including data from full testing of all quality attributes of at least 3 batches meeting specifications acceptance criteria per ICH Q7, 7.31. These data will be kept on site at Polarean and (b) (4). At least one batch with acceptance specifications by Polarean (b) (4) with CoA should be submitted to the NDA post-action.

Sent to Polarean:

PMC 2

- Polarean to describe supplier qualifying procedure and (b) (4) acceptance criteria (specification) for (b) (4) Xe-129 (enriched xenon gas) sourced through the (b) (4) supply chain. Include procedure and complete test results on site at (b) (4) and Polarean. Complete test results for 3 batches (b) (4) should be kept on site to qualify (b) (4) and future suppliers.



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- Amend the NDA post-action with complete test data for at least one batch from (b) (4). After qualification, (b) (4) may be accepted by Polarean/ (b) (4) by identity testing and inspection of supplier's CoA per ICH Q7 7.31. Submit a final report of the results as a Changes Being Effected Supplement (CBE-0).

a. Summary of Rationale for Recommendation:

Summary of Assessments (Product Quality):

There are many intricacies involved presenting challenges to the NDA review and which had led to the CR Letter of 10/05/2021. Critical for Drug Product Quality (CMC) is a range of factors that govern the amount of hyperpolarized ¹²⁹Xe (drug substance) produced and filling it into the collection bag (drug product as hyperpolarized ¹²⁹Xe in N₂) at a **dose equivalent (DE)** for patient administration, defined by the formula:

DE (in mL) = Xe 129 isotopic enrichment (%) x Xe volume (mL) x polarization (%), where % polarization = 100 x hyperpolarized Xe 129/total Xe 129.

Xe Volume – this is the volume of ¹²⁹Xe (total) (b) (4) (see Xenoview, Notes on Product Complexity in Section 5 under Additional Lifestyle Comments). The amount of hyperpolarized ¹²⁹Xe in this volume is in accordance the ratio (hyperpolarized ¹²⁹Xe / total ¹²⁹Xe). This ratio x 100 is defined as **% Polarization**. Proportioning with the % ¹²⁹Xe enrichment yields the DE.

Dovetailing off the expression for DE are the approvability issues identified for Drug Product CMC in Xenoview (delineated in the CR Letter of 10/05/2021) consisting of **(a) Degree of Polarization** (acceptance limits, acceptable variances, and justification through measurements from clinical batches produced with device (b) (4) in Phase 3 and that of the commercial (b) (4)

The second **(b)** approvability issue is the **Validation of the Production Method** (b) (4) and third **(c) Strength of the product** (in the bag) that is required for all pharmaceuticals under 21 CFR 314. [See Keynotes for explanations].

Following up there was an IR (October 13, 2022; requesting response by October 19, 2022) (b) (4)

relating to DP approvability-a in the 10/05/2022 action letter. This issue (a) along with (b) is **Resolved** (b) (4)

approvability issue (c) is also **Resolved.**

Another notable Drug Product issue had arisen (b) (4)



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[Redacted] (b) (4)

[Redacted] (b) (4)

Summary of Assessments (Process/Facilities):

The following is from Krishna Ghosh (12/05/2022), a High-Level Summary (Recommendations and Conclusion on Approvability).

The Hyperpolarized ^{129}Xe is the final drug product generated by the Xeno View System which is a combination device consisting of the following device components ^{129}Xe Hyperpolarizer, QC Measurement system and the dose delivery bag. The [Redacted] (b) (4)



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medical gas blend consists of enriched ¹²⁹Xenon (Xe- 1%v/v), Nitrogen (N₂-10% v/v) and Helium (He- 89% v/v) which is hyperpolarized by the Hyperpolarizer to produce the final drug product consisting of Hyperpolarized ¹²⁹Xe (b) (4) collected and measured by the QC measurement device in the dose delivery bag before being administered to the patient. Three manufacturing sites were re-inspected during the review of NDA 21437 resubmission (Resub-29) due to inadequate supporting evidence documents being provided in response to the FDA 483 and Post Action Letters issue to Polarean Inc (FEI# 3010132318), (b) (4)

(b) (4) The inspections in the current cycle at Polarean and (b) (4) group were acceptable (classified as VAI). (b) (4) PAI inspection was classified with an initial withhold through a recommendation was provided by field investigators and ORA PAM concurrence.

The major deficiencies noted (b) (4) during the re-inspection were due to (b) (4) (b) (4)

Critical issues (b) (4) that were identified in the (b) (4) DMF, impacting cGMP supplier qualification (b) (4) will be addressed in a Post Marketing Commitment (PMC # 4324-2). In summary, **all drug and device facilities and inspection issues are Resolved** (Final Integrated Manufacturing Assessment by Krishna Ghosh, 12/15/2022).

Keynotes (Product Quality):

(Analysis by ATL)

◆ **On Approvability Issues**

(b) (4)



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(b) (4)

Summary of Assessments (Labeling – CMC):

Established name of Drug Product (final) is not to be confused with ^{129}Xe (the Gas Blend) – **xenon-129 hyperpolarized**. Refer to “Xenoview, Notes on Product Complexity” under Section 5 (Life-Cycle Considerations). The final drug product composition ($\frac{(b)}{(4)}\%$ **hyperpolarized ^{129}Xe and $\frac{(b)}{(4)}\%$ N_2) of the effluent from the Polarean HPX Hyperpolarizer is filled into a patient administration bag for inhalation. [Reference is made to the previous Executive Summary (N214375-OPQ-EL-1308 in Panorama) for the chemistry behind production of hyperpolarized ^{129}Xe]. Based on the pertinent sections in N214375-OPQ-EL-1308 joint with discussions with Yana Mille, **the established name of the final drug product is agreed upon as xenon Xe 129 hyperpolarized**.**



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All issues regarding Prescribing Information (in package insert), Dose Bag Label, Gas Blend Cylinder Label, the Operator’s Manual and Quick Reference Guide are **Resolved** with labeling determined to be adequate from a drug product quality standpoint. Labeling Review – completed (Anne Marie Russell, 12/16/2022) - **Adequate**.

CONSULTS: to CDRH for device (Xenoview - combination product/device)
 The major device issue from the CR letter (10/05/2021) was the lack of performance of final device validation and manufacturing for (b) (4). Additionally, there was lack of device reliability assessment. All these issues have been resolved in the responses to the CR letter and there are no outstanding non-inspection related device concerns remaining. Accordingly, CDRH is **recommending approval** (email by Daniel Krainak, 8/31/2022).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

- Drug Substance - Adequate**
- Drug Product - Adequate**
- Quality Labeling - Adequate**
- Manufacturing - Adequate**
- Biopharmaceutics - N/A**
- Microbiology - N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Qualified Supply Chain and Distribution Plan:
 For Xenoview, there is the **Gas Blend**, (b) (4) composition (1% ¹²⁹Xe, 10% N₂, 89% He) packaged in a cylinder, supplied, and distributed by Polarean to sites that will use with the Polarean HPX Hyperpolarizer. The Gas Blend (in cylinder) is manufactured (b) (4) according to a set of established specifications.



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The chemical purity of the Gas Blend is (b) (4)%. The degree of enrichment in ^{129}Xe is > 80%. (b) (4) performs identity testing by GC-MS.

(Source of ^{129}Xe)[†]

Currently, the sole source is (b) (4) (b) (4) see PMC (page 3).

◆ Xenon Xe129 Gas Blend (b) (4)

The (b) (4) (Xenon gas, enrichment in ^{129}Xe) is obtained from (b) (4). It is delivered directly to (b) (4) manufacturing site. Xe is Element 54 in the Periodic Table, the same Group as He, chemically inert and exists as a gas. It is a trace element, extremely rare, considered the rarest of the inert gases, and expensive. Estimates of its natural abundance is variable likely due to the minuteness of quantities (primarily occurring in earth's atmosphere at one part in 20 million). Of the naturally abundant isotopes of Xenon, ^{129}Xe occurs at 26.401% exacerbating methodologies for enrichment to a level that must be exacted for successful production of hyperpolarized ^{129}Xe suitable in MRI. Consequently, there is a very limited number of suppliers from which Xenon gas at the necessary in ^{129}Xe can be obtained.

Assessment of Chemical Type and Drug Classification Code (ATL):

^{133}Xe and ^{127}Xe are the only Xenon isotopes currently approved (^{133}Xe , NDA 18327, approved 1982; ^{127}Xe , NDA 18536, approved 1982, but discontinued). Each of these isotopes of Xe are considered NME's (reference to section #5 in MAPP 5018.2). That ^{129}Xe falls in line as being an NME is based on MAPP 5018.2. **MAPP 5018.2 (official) specifies under Type 1 that "if a change in isotopic form....results in an active moiety that has never been approved by the FDA or marketed in the U.S., the active moiety is classified as an NME."**



N214375-OPQ-NME-RECOMMENDATION-

Xenoview, Notes on Product Complexity (ATL): From the Executive Summary (NB214375-OPQ-EL-1308 in Panorama) of the original NDA, the hyperpolarization is performed in an optical cell (1.9 L borosilicate glass cylinder with 85 mm diameter windows at the ends) in the Polarean HPX Hyperpolarizer.

(b) (4)



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(b) (4)

(Hyperpolarization). ¹²⁹Xe (gas) goes into the hyperpolarizer

(b) (4)

(b) (4)

(b) (4)

Reference is made to the Executive Summary (NB214375-OPQ-EL-1308 in Panorama) of the reviews of the original submission for a detailed discussion of the hyperpolarization process. **A brief summary of the chemistry of hyperpolarization is presented here:**

(b) (4)



Eldon
Leutzinger

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COMPLETE RESPONSE

Drug Product Information	Combination product drug/device
NDA Number/Type	N214375/ 505(b)(2)/Type 1/NME
Assessment Cycle Number	Review #2
Drug Product (DP) Name Strength	Xenoview (xenon Xe 129 hyperpolarized) DE ≥ 75mL per 1000 mL administered
Route of Administration Dosage Form Maximum Daily Dose	Inhalation Gas Not Specified
Applicant Drug Product Manufacturer	Polarean Durham, NC (b) (4)
RLD Information	No RLD. This 505(b)2 is by literature reference.
RLD/RS Number	
Proposed Indication	Contrast agent indicated for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation (b) (4) (b) (4) in adults and pediatric patients aged 12 years and older

Assessment Recommendation: Adequate

Assessment Summary:

The NDA is recommended as adequate from a CMC standpoint, pending resolution of the inspection and quality issues with DMF (b) (4)

An expiry of 5 minutes at 25°C for Xenoview (xenon Xe 129 hyperpolarized) is granted, based on stability data.

List Submissions Being Assessed:

Documents Assessed (EDR SEQ #)	Date Received	Description
28	March 30, 2022	Complete Response Resubmission Class 2
31	June 8, 2022	Response to CMC Information Request
32	July 22, 2022	Response to CMC Information Request
33	August 1, 2022	Response to CMC Information Request
34	August 5, 2022	Response to CMC Information Request
35	August 19, 2022	Response to CMC Information Request

DMF	Holder	Type	Description	Assessment
(b) (4)	(b) (4)	II	(b) (4)	Not acceptable. Facility withhold recommendation, additional quality issues. See DMF review.

Highlight Key Issues from Last Cycle and Their Resolution: Three key drug issues were identified by ONDP in the Last Cycle – #1 Drug Product Specifications (including attributes, analytical methods, and acceptance criteria with batch data), #2 Registration Batches and #3 Strength. These have been resolved in this review cycle, see review.

Concise Description of Outstanding Issues: DMF (b) (4) is not acceptable.

This is the second review cycle for Xenoview (Xenon Xe-129 hyperpolarized) for inhalation, a combination drug device product. This is a New Molecular Entity (NME) and the first of product its kind to be submitted for approval.

- Review Cycle #1: See ONDP review (04-Oct-2021) by Drs. C. Galliford/E. Leutzinger/D. Christodoulou for the initial assessment of the NDA, which covers the drug substance, the drug product and the manufacturing process. Refer to the OPMA review by Dr. Krishna Ghosh for the initial assessment of the facilities inspection. Refer to the CDRH review for the initial assessment of the device. The outcome of the first review cycle was a Complete Response Letter issued 5-Oct-2021 with deficiencies from ONDP (#1 - 3) and CDRH (#4 - 6).
- This Review #2 is limited to the ONDP deficiencies #1- 3 identified in the Complete Response Letter and additional drug review issues that arose in this review cycle. Information covered in Review #1 is not repeated here. See CDRH review for the CDRH deficiencies #4 – 6 and device issues addressed in this review cycle. A considerable amount of communication with the applicant was needed to address quality issues in this review cycle - five quality amendments were submitted to respond to four Information Requests with 20 comments. To keep this review succinct, all the Information Request comments were put in Appendix 1 and only the outcome and final assessment is captured in the review.
- Overview: The drug, Xenoview (xenon Xe 129 hyperpolarized) is produced on site by the HPX Polarization System from (b) (4) Xenon Gas Blend. The patient inhales the dose, the entire contents of the 1L Dose Delivery Bag, within 5 minutes of the final production step - measurement of the DE volume by the HPX Polarization Measurement Station. See figure.

Primary Drug Product Assessor Name and Date:

Anne Marie Russell, Ph.D. Drug Product Reviewer 31-Aug-2022

Secondary Assessor Name and Date:

Eldon Leutzinger, Ph. D. Senior Pharmaceutical Quality Assessor 31-Aug-2022



Anne
Russell

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FINAL RECOMMENDATION OF DRUG PRODUCT REVIEW: APPROVAL

Drug Product Information	Combination product drug/device
NDA Number/Type	N214375/ 505(b)(2)/Type 1/NME
NDA Assessment Cycle Number	#2 (Resubmission after Complete Response) Clock Extension to Dec 30, 2022.
CMC Review Number	#3
Drug Product (DP) Name Strength	Xenoview (xenon Xe 129 hyperpolarized) DE ≥ 75mL per 1000 mL administered
Route of Administration Dosage Form Maximum Daily Dose	Inhalation Gas Not Specified
Applicant Drug Product Manufacturer	Polarean Durham, NC (b) (4)
RLD Information RLD/RS Number	505(b)2 by literature reference. See clinical review in DARRTS.
Proposed Indication	Contrast agent indicated for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation (b) (4) in adults and pediatric patients aged 12 years and older

Assessment Recommendation: Adequate

Assessment Summary:

The NDA is recommended for approval from a CMC standpoint.

An expiry of 5 minutes after final Dose Equivalent (DE) measurement at 25°C for Xenoview (xenon Xe 129 hyperpolarized) is granted, based on stability data. The Applicant proposed and the OND clinical team confirmed that the patient ventilation procedure can be executed by the Polarean trained technician within 5 minutes of DE measurement.

List Submissions Being Assessed:

Documents Assessed (EDR SEQ #)	Date Received	Description
37	Sept 27, 2022	90 day clock extension request and response to action item from tcon#1: Homogeneity Stability - Phase 3 clinical study DP lot data
39	Oct 19 2022	Response to IR#5 re-tested (b) (4) lots
40	Dec 07, 2022	Updated (b) (4) specifications Xe 129 identity

DMF	Holder	Type	Description	Assessment
	(b) (4)	II	(b) (4)	Acceptable with Post Marketing Commitment for (b) (4) (enriched Xe-129) supplier qualification. See DMF review #2 by Anne Marie Russell, Ph.D in Panorama, Dec 15, 2022. See PMC# 4324-2 in DARRTS.

Highlight Key Issues from Last Cycle and Their Resolution:

The DMF holder and NDA Applicant have worked together under mutual Letters of Authorization (LOAs) during the clock extension to resolve the DMF issues, except for the issue of (b) (4) (enriched Xe-129) supplier qualification which remains outstanding and will be addressed in PMC # 4324-2. See DMF review #2 archived in Panorama Dec 15, 2022. See PMC# 4324-2 in DARRTS.

Concise Description of Outstanding Issues: PMC 4324-2

CMC REVIEW #3

Introduction and Background:

This review #3 is an assessment of the CMC issues with NDA 214375 that have been addressed during the clock extension, since review #2 was archived in Aug 30, 2022. See DMF review #2 in Panorama for an assessment of the CMC issues with DMF (b) (4) that have been addressed during the clock extension.

To facilitate resolving the DMF issues from the (b) (4) manufacturing and release site PAI inspection and the ONDP review, Letters of Authorization were issued by both parties to authorize teleconference discussions between (b) (4) and Polarean related to Polarean’s NDA and (b) (4) manufacturing activities. On Sept 30, 2022, a 3-month clock extension was granted due to submission of a major amendment (b) (4) to their DMF (b) (4) extending the NDA PDUFA clock to Dec 30, 2022.

Four teleconferences were held on 9/20, 10/21, 11/18 and 12/9. The Polarean action items from those teleconferences are archived in the internal memos and meeting minutes in DARRTS, see DARRTS. See DMF review for the (b) (4) IRs and tcon action items and responses, which overlap ONDP and OPMA/inspection (b) (4) issues. Polarean responses to the action items are reviewed in detail below.

Teleconferences Held Jointly with (b) (4) and Polarean			
Tcon	Date of teleconference	Topics	Documented in DARRTS as
#1	September 20, 2022	(b) (4) IR#2. Major amendment. Joint assessment tcons.	Internal memo
#2	October 21, 2022	Status response to (b) (4) IR#2 and IR#3.	Meeting minutes
#3	November 18, 2022	Clarification response to (b) (4) IRs, 8 action items (b) (4) to submit	Meeting minutes
#4	December 9, 2022	Final wrap-up. Post Marketing Commitment for (b) (4) (Polarean)	Internal memo

Labeling:

For labeling, the CMC review of the PI, Operator’s Manual, Dose Delivery Bag and Gas Blend Cylinder is complete but the final labeling has not been negotiated with Polarean at this time.

Final Assessment:

The outcome of the evaluation of IR responses received from (b) (4) and Polarean up to December 7, 2022, is that the DMF is acceptable and the NDA is recommended for approval with a Post Marketing Commitment #4324-2 to address the outstanding cGMP supplier qualification of (b) (4) enriched Xe-129. On Dec 15, 2022, Polarean agreed to PMC #4324-2 which is documented below. OPMA will review the fulfillment of PMC #4324-2.

Review Issues:

Brief Overview of the Product: Xenoview (xenon Xe 129 hyperpolarized) for inhalation is a drug/device combination product. It is produced by the device HPX Hyperpolarizer System from the (b) (4) Xenon Xe 129 Gas Blend (containing 1% Xe-129 and 10% Nitrogen) at the clinical site. (b) (4) manufactures the HPX Hyperpolarizer. (b) (4) manufactures (b) (4) (b) (4) under DMF (b) (4)

(b) (4)

Primary Reviewer:

Anne Marie Russell, Ph.D. CMC Reviewer OPQ/ONDP/DNDPIII/Branch 6

Secondary Reviewer:

Danae Christodoulou, Ph.D. Branch Chief OPQ/ONDP/DNDPIII/Branch 6



Anne
Russell

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Christodoulou

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CHAPTER IV: LABELING

The Prescribing information, Operator’s Manual, Quick Reference Guide, Dose Bag, Dose Bag Carton and Gas Blend Cylinder label versions as of Dec 15, 2022 were reviewed. Labeling negotiations with Polarean were not final at the time of this review, but CMC comments and edits were complete.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	Xenon Xe 129 hyperpolarized. This established name meets USP nomenclature for isotopes. The labeling team in OPPQ finalized this established name in 2021. See CMC review #1 dated Oct 4, 2021 in Panorama.
Route(s) of administration	Adequate	for oral inhalation
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Dose form is gas. Strength is DE/L where DE is the dose equivalent, defined below, and L is volume of gas administered (1.000 liters). DE is a value calculated from the isotope enrichment and the degree of polarization. DE is the volume in mL of 100% hyperpolarized, 100% isotopically enriched xenon Xe 129 which would provide the equivalent total Xe 129 magnetization (or MRI signal). The HPX Polarization Measurement Station measures DE.

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

		DE is defined by the following formula: $DE = (\text{total volume xenon gas}) \times (\text{fraction of xenon Xe 129 isotopic enrichment in the xenon gas}) \times (\text{fraction of hyperpolarization})$ OPPQ labeling team deferred strength determination to the review team for review team's expertise. See Review #1, Oct. 4, 2021.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	This is not a tablet dosage form.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not applicable.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)

DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Section 2.2 of the PI describes the Preparation, Administration, and Image Acquisition.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Section 2.2 of the PI describes the Preparation, Administration, and Image Acquisition.
For parenteral products: include statement: <i>“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	The isotope Xe 129 is stable.

For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.”</i>^x with x numerical citation to <i>“OSHA Hazardous Drugs”</i>.	N/A	The gas is not hazardous.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	gas
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	clear, colorless, odorless gas
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	XENOVIEW (xenon Xe 129 hyperpolarized)
Dosage form(s) and route(s) of administration	Adequate	gas for oral inhalation
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not a salt.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	"Contrast agent" under negotiation between applicant with clinical team at this time.
Chemical name, structural formula, molecular weight	Adequate	

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state “DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.” with x numerical citation to “OSHA Hazardous Drugs.”	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “<i>Not made with natural rubber latex. Avoid statements such as “latex-free.”</i>”	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling: None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Following is included: Manufactured for: Polarean, Inc. 2500 Meridian Parkway, Suite 175 Durham, NC 27713

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): NONE

Operator's Manual and Quick Reference Guide have been assessed by interdisciplinary review team. Acceptable.

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Dose Bag label (not final)



(b) (4)

Gas Cylinder label (not final)

(b) (4)



3.2 Carton Labeling
Dose Bag Carton (not final)

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ² , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	N/A	Not a salt.
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	N/A	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Product is administered in hospitals, imaging centers and not dispensed to a patient.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

² Established name = [Drug] [Route of Administration] [Dosage Form]

Overall Assessment and Recommendation:

At the time of review, OND labeling negotiations were ongoing. The CMC review, edits and comments were final. The version of Prescribing Information, operator's manual, quick reference guide, dose bag label and gas blend cylinder labels reviewed are adequate from a product quality perspective.

Primary Labeling Assessor:
Anne Marie Russell, Ph.D.

16-Dec-2022

Secondary Assessor
Danae D. Christodoulou, Ph.D.

16-Dec-2022



Anne
Russell

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Danae
Christodoulou

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12/20/2022 10:59:39 AM

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Recommendation: **Complete Response**

NDA [214375]

Xenoview

Review #[FINAL]

Drug Name/Dosage Form	Xenoview (xenon-129 hyperpolarized)
Strength(s)	Not defined. Applicant proposes a target dose of 75 mL dose equivalent of hyperpolarized Xe-129 (b) (4)
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	Polarean Inc.
US agent, if applicable	Facet Life Sciences, Apex, NC 27523

SUBMISSION(S) REVIEWED (seq. no.)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 214375 (000)	10/05/2020	OPQ-CMC, Microbiology, Manufacturing Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Christopher Galliford	Eldon E. Leutzinger for Danae Christodoulou
Drug Product	Danae Christodoulou (to finish for Christopher Galliford, former FDA reviewer)	Eldon E. Leutzinger for Danae Christodoulou
Process/Facilities	Krishna Ghosh	Vidya Pai
Microbiology	Samata Tiwari	Neal Sweeney
Environmental	Christopher Galliford	Eldon E. Leutzinger for Danae Christodoulou
RBPM	Anika Lalmansingh	N/A
Application Technical Lead	Eldon E. Leutzinger	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	8/26/2021	N/A

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND (Polarean, Inc.)	75010	Hyperpolarized ¹²⁹ Xe

2. CONSULTS

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
N/A			

Executive Summary

I. Overall Recommendation on Approvability

OPQ recommends [COMPLETE RESPONSE] of NDA [214375] for commercialization of [Xenoviev/xenon-129 hyperpolarized/formulation - one Liter of gas made up of (b) (4) xenon-129 and (b) (4) nitrogen/strength not defined – applicant proposes a DE with target dose of 75 mL (b) (4) hyperpolarized xenon-129 in I L] with an expiration dating period (b) (4)

- The applicant [has not] provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product, as is discussed in this executive summary.
- The Office of Process and Facility has made a recommendation of [withhold] for (b) (4) (b) (4) and Polarean Inc. The preapproval inspection of (b) (4) has received an OAI – (Official Action Indicated). Details of these actions are provided in this executive summary (page 11 and 12).
- The proposed labeling and labels [do not have] adequate information to meet the regulatory requirements, as discussed in this executive summary.

II. Product Quality Review Context

Indication and Intended Population: diagnostic agent for used with MRI (b) (4)
(b) (4)

Regulatory Context - Designation of Drug Substance: The Drug Substance is designated as ^{129}Xe , the determination of which is explained in the following document (b) (4)
(b) (4)



N214375-OPQ-NME-
RECOMMENDATION-

(b) (4)

Rationale for Determination

Analysis by ATL:

(b) (4)

Product Profile and Critical Quality Attributes (CQA's):

(b) (4)

(b) (4)

Refer to Regulatory

Context – Designation of Drug Substance and the Rationale for Determination by ATL.

(Product Dose)

So, the product (which is inhaled by patients, the dose) is a 1 L volume of gas (hyperpolarized ^{129}Xe) and q.s.'d with $^{129}\text{Xe}^*$ (b) (4) 75 mL) is $^{129}\text{Xe}^*$ (hyperpolarized ^{129}Xe) and q.s.'d with (b) (4) N_2 . In terms of percentages, the target dose is (b) (4) % hyperpolarized ^{129}Xe and (b) (4) % N_2 .

1.3. Final Drug Product

The commercial drug product is a gaseous blend of helium (89%), nitrogen (10%), and isotopically enriched Xe ($\geq 80\%$ in ^{129}Xe [1%]). It is processed in the hyperpolarizer device component to polarize the ^{129}Xe atoms and remove the helium and nitrogen, thus yielding ^{129}Xe gas, polarized to (b) (4)%, to be diluted with nitrogen NF for administration. The total gas volume for administration of the final drug product is 1 L. The standard volume (dose) of hyperpolarized ^{129}Xe is 75 mL polarized ^{129}Xe dose-equivalent (up to 750 mL total Xe volume) administered (via inhalation) to the subject while in the MRI. The composition of the ^{129}Xe final drug product for patient administration is shown in Table 5.

Table 5 Component and Composition of the ^{129}Xe Gas Blend Final Drug Product

Component	Composition	Amount	Function	Quality Standard
Hyperpolarized ^{129}Xe	(b) (4)	(b) (4) mL total Xe	Active pharmaceutical ingredient	In House
Nitrogen, NF		qs to volume	(b) (4)	99.9999% purity
Total	100%	1 L		

Abbreviations: NF = National Formulary.

Analysis by ATL:

(b) (4)

(b) (4)

**Labeling**

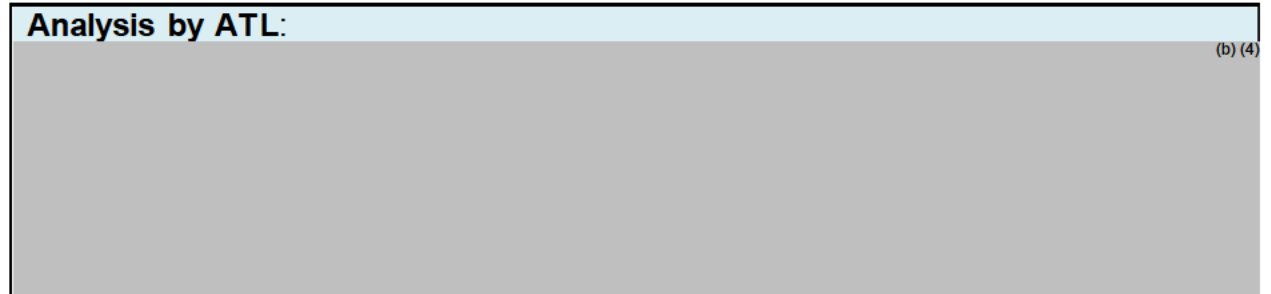
There are two issues for labeling. The first (1) is the established name. A recommendation has been made for this and is provided in the following email from Jabril Abdus-Samad (CDER/OPQ/OPPQ/COSS). That recommendation for the established name is “**xenon-129 hyperpolarized**.”



RE_Hyperpolarized
Xe-129_NDA 214375.

Analysis by ATL:

(b) (4)





(b) (4)

Microbiology



RE_ NDA 214375_
Hyperpolarized 129-X



response-to-informat
ion-request.pdf

(response to 4/22/2021 IR)

Based on the responses (above (b) (4) right panel), all microbiology issues are **Resolved**.

Facilities

The following is the assessment of facilities from Krishna Ghosh, Ph.D. (9/30/2021):

Facility Assessment Recommendation: Inadequate

High Level summary:

Polarean Inc. (FEI:3010132318) is the applicant and design and specification developer for the XenoView System and is also responsible for manufacturing of all the device components for the XenoView System. Polarean has contracted (b) (4) (b) (4) for commercial production of the device components which are the ¹²⁹Xe Hyperpolarizer, Measurement system and the dose delivery bags. (b) (4) will be responsible for providing the medical gas blend with the approved quality specifications under this NDA application.

The preapproval inspection (b) (4) was classified as (OAI- Official Action Indicated) due to several product specific deficiencies (b) (4) (b) (4)



The preapproval inspections at (b) (4) Polarean Inc. are recommended for withhold by Office of Process and Facility and CDRH (b) (4) (b) (4)

(b) (4)

Facility CR :

1. During a recent inspection of the Polarean Inc. (FEI:3010132318) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
3. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

IV. Final Analysis of Product Quality Review Issues (~200 words per issue)

There are two issues remaining from the primary review for CMC (Chemistry, Manufacturing and Controls) Product Quality. (b) (4)

(b) (4)

(b) (4)

V. Summary Basis for Product Quality Recommendation (150 words)

Xenoview does not meet applicable standards to support the identity, strength, quality and purity. From a product quality standpoint, the recommendation is a CR.

VI. Lifecycle Considerations

There are no important future lifecycle considerations.



Eldon
Leutzinger

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MICROBIOLOGY

Product Information	Indicated for use in conjunction with MRI (b) (4) (b) (4)
NDA Number	214375
Assessment Cycle Number	01
Drug Product Name / Strength	Hyperpolarized ¹²⁹ Xe
Route of Administration	Inhalation
Applicant Name	Polarean Inc.
Therapeutic Classification/ OND Division	CDER/OND/ODEIV/ Division of Medical Imaging Products
Manufacturing Site(s)	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: Adequate

Assessment Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions Being Assessed

Document(s)	eCTD	SDN	Date Received
NDA-214375-ORIG-1	0001	1	10/05/2020
Multiple categories	0002	3	01/15/2021
Quality Response	0005	6	02/26/2021
Quality Response	0008	9	03/11/2021
Quality Response	0013	13	05/03/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues: None.

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

The drug product is a non-sterile gas blend consisting of enriched Xenon, Nitrogen and Helium. The gas blend is supplied in aluminum cylinders as a compressed gas under high pressure (2105 pounds per square inch [psig]) in size 302 aluminum cylinders.

Drug product composition

Component	Amount	Function	Quality Standard
Isotopically Enriched Xenon ¹	1% v/v	Active Ingredient	In House ²
Nitrogen, NF (99.999% purity)	10% v/v	(b) (4)	NF + In House ³
Helium, NF ((b) (4)% purity)	89% v/v	(b) (4)	NF + In House ⁴

Abbreviations: NF = National Formulary.

¹ Enriched Xenon gas contains NLT 80% ¹²⁹Xe.

The drug product gas blend is hyperpolarized to generate the final drug product for inhalation. The hyperpolarization process

(b) (4)
(b) (4)

(b) (4) The final drug product gas blend consists of non-sterile, polarized ¹²⁹Xe atoms and N₂ excipient in a single use Dose Delivery Bag (final drug product/device combination) with a single use mouthpiece.

The Xenon Hyperpolarizer System is a drug-device combination product. The figure below shows the drug and device components of the system.

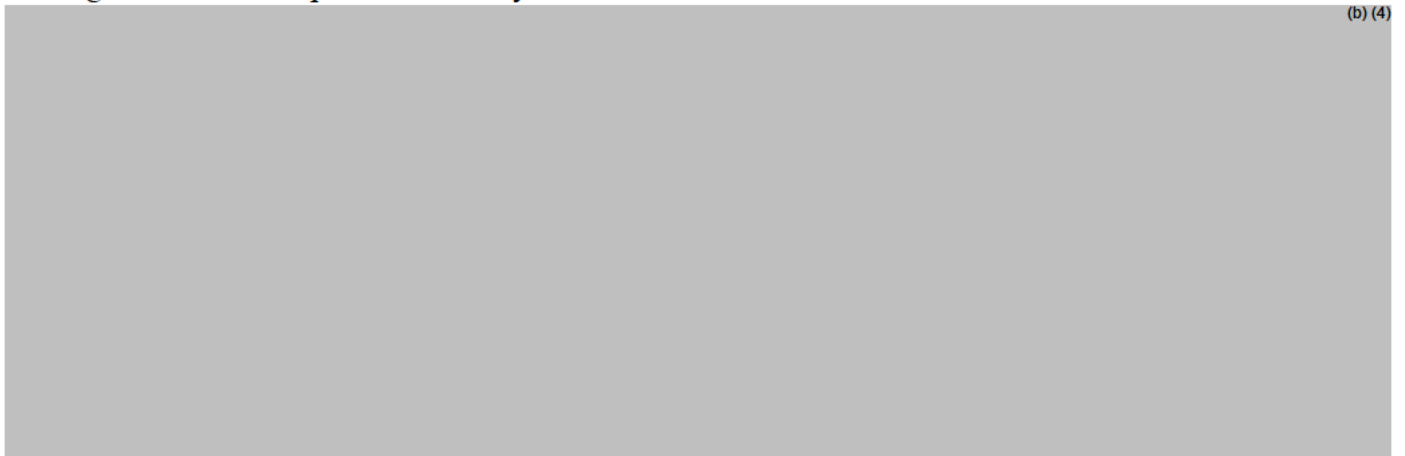


Figure 1: Polarean Xenon Hyperpolarizer System Drug–Device Components

Final drug product/device combination: Non-sterile hyperpolarized ^{129}Xe drug product in a non-sterile single use delivery bag with a non-sterile single use mouthpiece and (b) (4) tube.

Description of container closure system

Xenon Gas Blend Container Closure System:

The container closure system for the pre-hyperpolarized gas blend is a size 302 aluminum gas cylinder with brass valve.

Hyperpolarized ^{129}Xe Gas Container Closure:

The final container closure system for the hyperpolarized ^{129}Xe gas is a 1 L perfluoropolymer (Tedlar®) delivery bag that is affixed with a mouthpiece prior to delivery to the patient. The Tedlar bag and mouthpiece serve both as a container closure system and drug delivery device. The Dose Delivery Bag is a component of the Xenon Hyperpolarizer System.

The Dose Delivery Bag components include (A) sealed mouthpiece, (B) Main (Tedlar) bag, (C) (b) (4) tubing, and (D) tube pinching clamp (Figure 1). The Dose Delivery Bag provides an open tube on one end to attach a mouthpiece for delivering the dose to the patient. The only patient-contacting component of the Xenon Hyperpolarizer System is the Dose Delivery Bag. The Dose Delivery Bag is made of (b) (4) clear, sealable Tedlar. The bag features a mouthpiece made of (b) (4) that connects to the bag via tubing made of (b) (4) tubing. The mouthpiece is intended to come in contact with the patient for a limited amount of time (< 24 hours, usually under 1 minute). The Dose Delivery Bag is used to contain the dispensed hyperpolarized ^{129}Xe from the Xenon Hyperpolarizer once collection is completed. The bag can then be transported to the Polarization Measurement Station to record the polarization level, before subsequently being delivered to the patient for administration. The Dose Delivery Bag is provided in a pre-assembled format, with only the need to attach the mouthpiece prior to use. The Dose Delivery Bag is shown in the figure below:

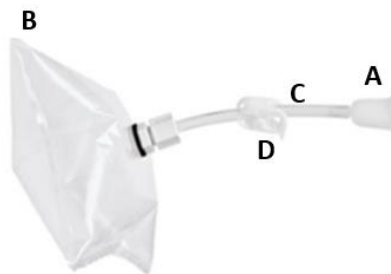


Figure 1: One-liter Dose Delivery Bag and key components: A) mouthpiece, B) Tedlar bag, C) (b) (4) tube and D) pinch valve.

Dose Delivery Bag Specifications:

(b) (4)

Assessment: Adequate

The Applicant has provided an adequate description of the drug product composition and the container closure system

The following information request was provided to the applicant in the Filing Communication Letter dated 18 December 2020.

(b) (4)

The applicant forwarded response on 01/15/2021 reviewed below:

(b) (4)

(b) (4)

Applicant's response (05/03/2021):

(b) (4)

(b) (4)

Assessment: *Adequate*

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

P.3 MANUFACTURE

(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES

(None)

Primary Microbiology Assessor Name and Date:

Samata Tiwari, Ph.D., 06/08/2021

Microbiologist

CDER/OPQ/OPMA/DMA I/Branch 2

Secondary Assessor Name and Date:

Neal Sweeney, Ph.D., 06/09/2021

Senior Pharmaceutical Quality Assessor

CDER/OPQ/ OPMA/DMA I/Branch 2



Samata
Tiwari

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Neal
Sweeney

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